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Regulatory challenges for autologous tissue engineered products on their way from bench to bedside in Europe ☆

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ABSTRACT

Since the late eighties of last century the high potential of tissue engineered products (TEP)s has been shown for the treatment of various diseases and many scientific publications appeared in this field. However, only few products reached the market since. Development of TEPs is a promising but owing to its novelty a very challenging task that requires experts in this still developing field as well as ample financial resources. This paper summarises relevant regulatory challenges during quality, preclinical and clinical development of autologous TEPs in Europe. Selected strategies on how to manage major issues are presented, together with some examples from the development of an autologous TEP for urethroplasty. Considering these aspects may help other investigators with potential strategies during the development of novel TEPs.

Contents

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1. Introduction

In Europe TEPs, somatic cell therapy medicinal products, and gene therapy medicinal products are summarised under the term advanced therapy medicinal products (ATMP) [1,2]. TEPs contain viable autologous, allogenic or xenogenic cells. While somatic cell therapy medicinal products are intended to treat or prevent a disease or to make a diagnosis through pharmacological, metabolic, and/or immunological action, the claim of TEP is to regenerate, repair, or replace human tissue [1,2]. TEPs are based on living cells and may additionally contain natural or synthetic extracellular components. Due to availability and regenerative capability of cells, tissue engineering (TE) presents new opportunities for physicians to help patients in various indications.

Scientific congresses or symposia on TE have been organized more than twenty years ago. An annually increasing number of scientific papers on this topic appeared since [3]. However assessment of quality, safety, and efficacy of these novel products is challenging, because methods and procedures established for conventional pharmaceutical products and biologics are often inappropriate for them. Therefore, up to now very few TEPs are available for clinical use [3]. To date, in Europe only two TEPs have been authorised centrally for all Member States (Table 1). Both products contain autologous cartilage cells and are used in adults to repair damage of the cartilage in the knee. One, ChondroCelect, is a TEP indicated for repairing single symptomatic cartilage defects of the femoral condyle of the knee in adults. It is a suspension of cultured autologous cartilage cells. The second, MACI, is a combined ATMP indicated for the repair of symptomatic, full thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3–20 cm^2 in skeletally mature adult patients. It consists of autologous cartilage cells cultivated on a collagen membrane. ChondroCelect is secured at the implantation site by a biological membrane such as a periosteal flap. A type of glue known as a fibrin sealant, which is made from blood clotting proteins, is used.to hold MACI in place on the cartilage.

In addition to these TEPs, each one somatic cell therapy medicinal product and one gene therapy medicinal product have been authorised (Table 1).

While first TEPs for cartilage repair have received centralised marketing authorisation for Europe, further products for orthopaedic and trauma surgery are expected on the market. Madry *et al.* recently published the main results of a symposium held with more than one hundred stakeholders involved in clinical translation of orthopaedic TE, including scientists, clinicians, healthcare industry professionals, and regulatory agency representatives [4]. The aim was to address barriers that are associated with the translation of new applications from research in orthopaedic TE and to discuss strategies to overcome them.

This paper presents main regulatory requirements that have to be met in order to obtain marketing authorisation for TEPs in Europe. Beside general recommendations, some examples from the development of our product MukoCell®, a tissue-engineered oral mucosa graft (TEOMG), are mentioned. This paper should be considered as assistance for TEP developers for managing regulatory challenges. However one should consider that a general road map for the clinical translation of TEPs does not exist due to the high heterogeneity between them.

MukoCell® consists of autologous somatic oral mucosa cells, cultured on a biodegradable scaffold. Worldwide, it is the first nationally authorised urologic ATMP product, legally marketed in Germany according to section §4b AMG (German Drug Law) with the authorisation number PEI.A.11491.01.1 In addition, the quality and pre-clinical data of this product have been certified by the European Medicines Agency (EMA). The certificate confirms that the quality of the submitted data meet the current scientific and regulatory requirements of EMA. Currently we are on our way to fulfil last outstanding requirements for European marketing authorisation, namely a pivotal phase III randomized multicentre clinical trial.

The activities of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) ensure mutual recognition of many aspects of medicinal product development between Europe, the US and Japan.

2. Legal framework for TEPs

The European Parliament and the Council of the European Union have decided that all ATMP including TEPs should be regulated in a consistent manner throughout all Member States. Therefore a specific regulation for ATMP was adopted that has introduced the following definitions for TEPs and engineered cells [1]:

ATMP may contain cells or tissues of human or animal origin, or both. The cells of tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Cells or tissue shall be considered 'engineered' if they fulfil at least one of the following conditions:

- the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological function or structural properties relevant for the intended regeneration, repair or replacement are achieved.
- the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Since 30 December 2008, a centralised marketing authorisation is mandatory for ATMPs including TEPs in all European Member States. A transitional period for TEP that were already on the market at that time, elapsed by the end of 2012.

Marketing authorisation application for TEPs is processed by EMA. At the EMA, the Committee for Advanced Therapies (CAT) has been established. This committee is responsible for assessing the quality, safety and efficacy of ATMPs and also provides the procedure of ATMP classification [5]. According to the abovementioned definition, classification

Table 1
Advanced therapy medicinal products for which centralized marketing authorisation has been granted in Europe.

Product name	Type of product	Active substance	Intended use
ChondroCelect	Tissue engineered product	Suspension for implantation that contains cartilage cells	Used in adults to repair damage to the cartilage in the knee
MACI	Tissue engineered product	Cartilage cells	Used to repair cartilage defects at the ends of the bones of the knee joint
Glybera	Gene therapy product	Alipogene tiparvovec (engineered copy of the human LPL gene packaged with a non-replicating AAV1 vector)	Used to treat adults with lipoprotein lipase deficiency
Provenge	Somatic cell therapy product	Peripheral blood mononuclear cells activated with PAP-GM-CSF	Used to treat adult men with cancer of the prostate